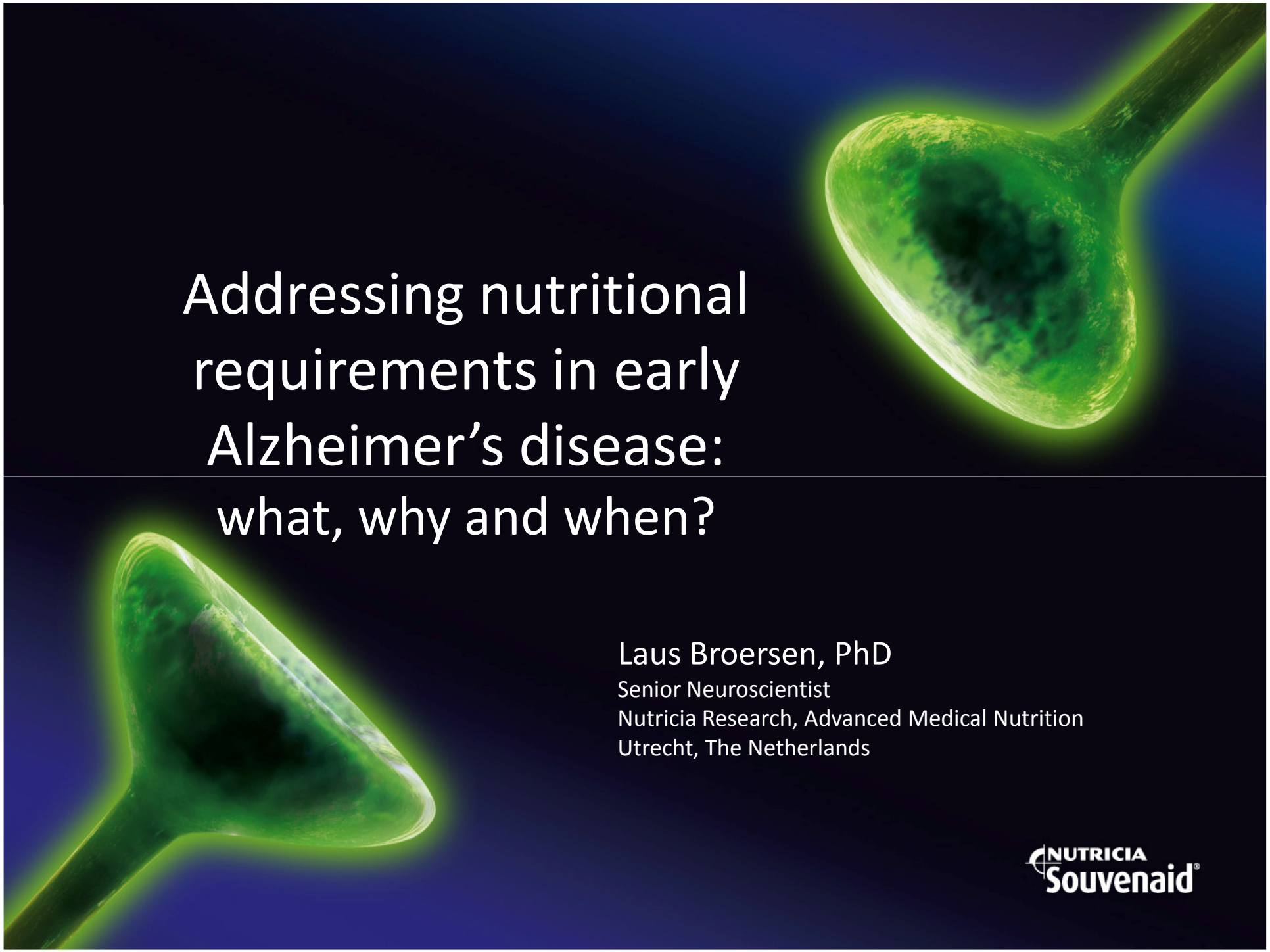
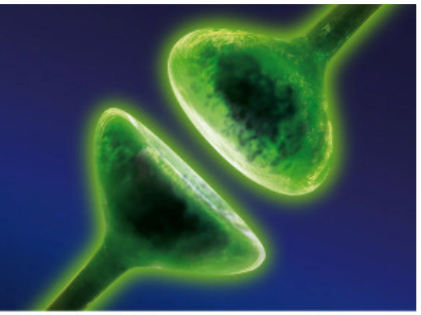
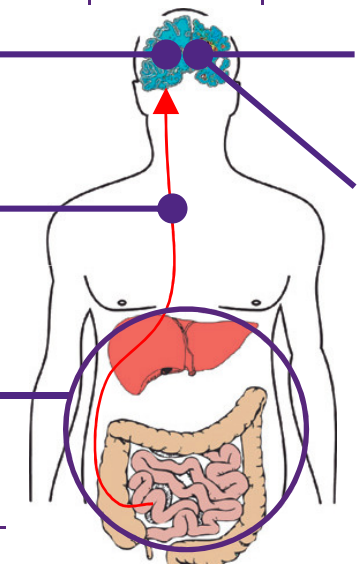

Addressing nutritional requirements in early Alzheimer's disease: what, why and when?
Laus Broersen, PhD
Senior Neuroscientist
Nutricia Research, Advanced Medical Nutrition
Utrecht, The Netherlands
NUTRICIA
Souvenaid®

AD specific nutritional needs for membrane and synapse formation



1 AD-induced compromised nutrient availability

- A Lower brain nutrient levels
- B Lower blood nutrient levels
- C Lower nutrient intake, uptake and metabolism



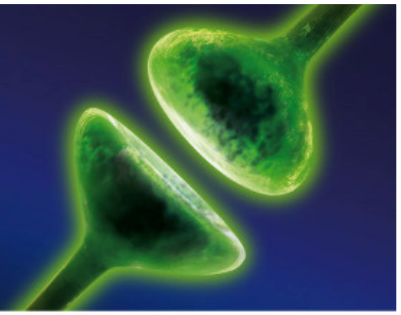
2 In AD a specific need exists to enhance synapse formation

- A Patients with AD show lower number of brain synapses
- B Patients with AD show lower level of neuronal membranes
- C Membrane and synapse formation dependent on nutrient availability

3 AD specific nutrient requirement to meet the increased demand for synapse formation

4 **Souvenaid** addresses the nutritional need to support increased synapse formation in patients with AD

Synapse loss is structural basis of functional deficits in AD

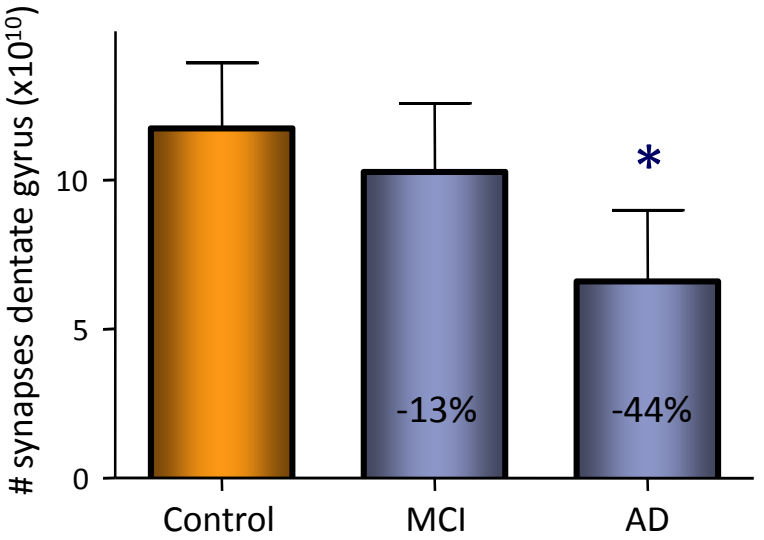


Physical Basis of Cognitive Alterations in Alzheimer's Disease: Synapse Loss Is the Major Correlate of Cognitive Impairment

Robert D. Terry, MD,* Eliezer Masliah, MD,* David P. Salmon, PhD,* Nelson Butters, PhD,†
Richard DeTeresa, BS,* Robert Hill, PhD,* Lawrence A. Hansen, MD,* and Robert Katzman, MD*

Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R.
Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol 1991;30:572–580

Reduced number of synapses



VIEWPOINT

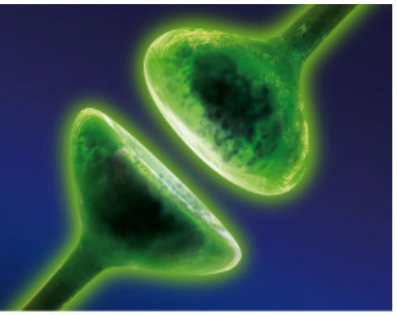
Alzheimer's Disease Is a Synaptic Failure

Dennis J. Selkoe

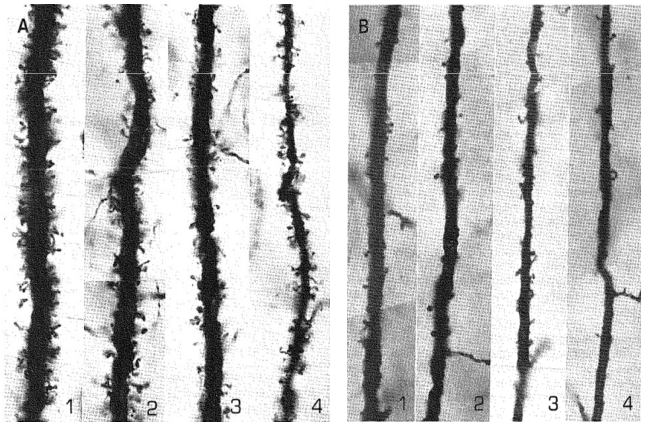
SCIENCE VOL 298 25 OCTOBER 2002

Synapse loss in AD is confirmed in >30 publications

Loss of dendritic spines in AD

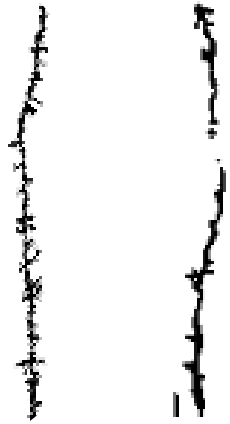


Control AD



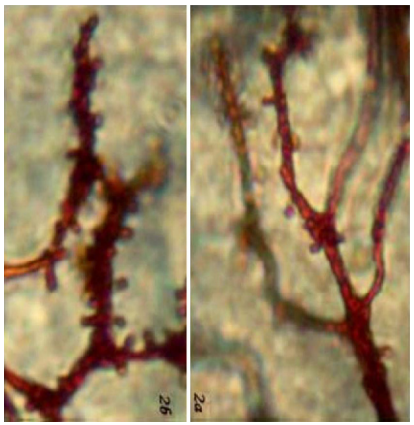
Catala et al (1988)
Hum Neurobiol

Control AD



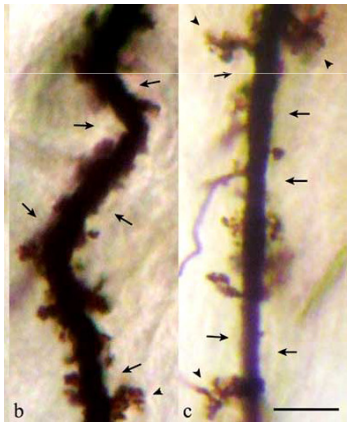
Einstein et al (1994)
J Neurosci

Control AD



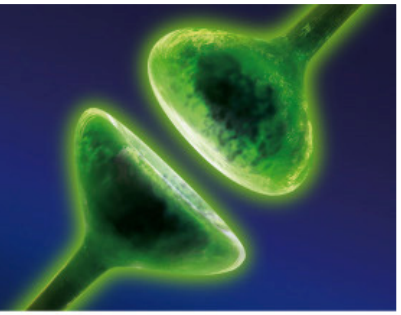
Mavroudis et al (2010)
Am J Alz Dis oth Dement

Control AD



Tsamis et al (2010)
Curr Alzheim Res

Decreased brain phospholipids in AD indicates disrupted membrane integrity



Int. J. Mol. Sci. **2013**, *14*, 1310-1322; doi:10.3390/ijms14011310

Review

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ISSN 1422-0067
www.mdpi.com/journal/ijms

Phospholipids and Alzheimer's Disease: Alterations, Mechanisms and Potential Biomarkers

Marko Kosicek and Silva Hecimovic *

Table 1

Phospholipid changes in the brain of individuals with Alzheimer's disease.

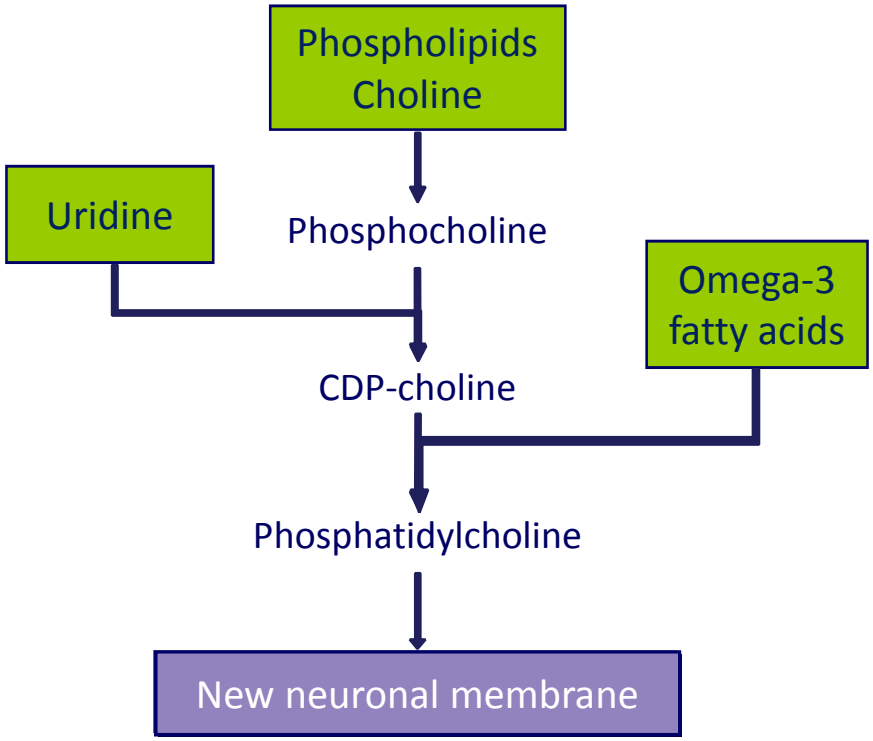
Lipid class	Change/Normalization	Sample size/Examined brain regions/Analytical method	Reference
PI	decreased/wet weight	9 AD and 9 controls/HPG, SMTG, IPL and cerebellum/TLC	[14]
PI	decreased/wet weight	17 AD and 18 controls/anterior temporal cortex/TLC	[15]
PI	decreased/relative	45 AD and 11 controls/SMFG, STG, IPL, occipital cortex and cerebellum/^{31}P NMR	[21]
PE	decreased/wet weight	9 AD and 9 controls/HPG, SMTG, IPL and cerebellum/TLC	[14]
PE	decreased/DNA	10 AD and 10 controls/frontal, primary auditory and parietal cortex/photometrical phosphorus determination	[16]
PPE	decreased/relative	9 AD and 9 controls/middle-temporal cortex/HPLC and TLC	[18]
PPE	decreased/phosphate	15 AD and 13 controls/frontal cortex, hippocampus and white matter/HPLC and GC	[19]
PPE	decreased/relative	45 AD and 11 controls/SMFG, STG, IPL, occipital cortex and cerebellum/^{31}P NMR	[21]
PPE	decreased/protein	6 CDR = 0; 6 CDR = 0.5; 6 CDR = 1; 6 CDR = 2; 6 CDR = 5/white and gray matter from SFG, STG, IPL and cerebellum/ESI-MS	[22]
PC	unchanged/wet weight	9 AD and 9 controls/HPG, SMTG, IPL and cerebellum/TLC	[14]
PC	decreased/DNA	10 AD and 10 controls/frontal, primary auditory and parietal cortex/HPLC–fluorimetric detection	[16]
PC	unchanged/wet weight	6 AD and 4 controls/gray matter from frontal cortex, parietal and temporal region/HPLC	[17]
PC	decreased/phosphate	15 AD and 13 controls/frontal cortex, hippocampus and white matter/HPLC and GC	[19]

4. Conclusions

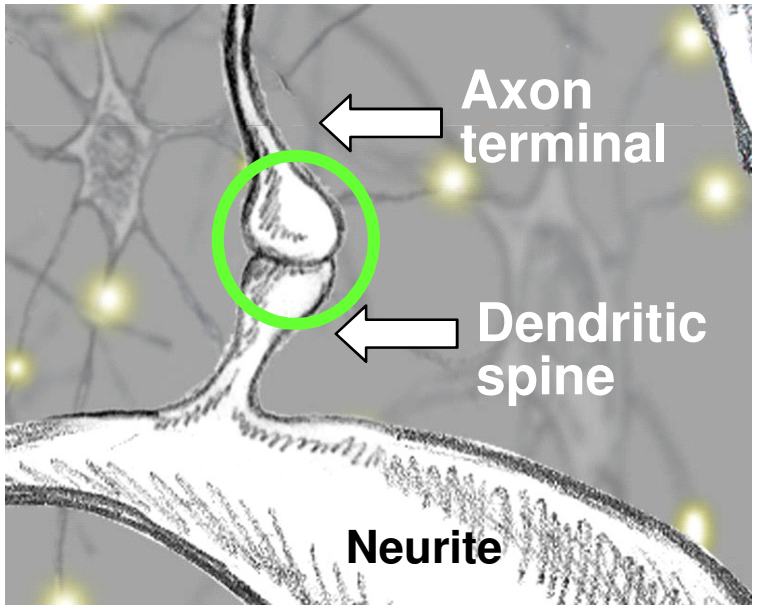
"… Phospholipids provide an optimal membrane environment for protein interactions, trafficking and function. There is increasing evidence that phospholipid changes occur during pathogenic processes in Alzheimer's disease. …"

Dietary precursor control of neural membrane synthesis

The Kennedy pathway for biosynthesis of neuronal membrane

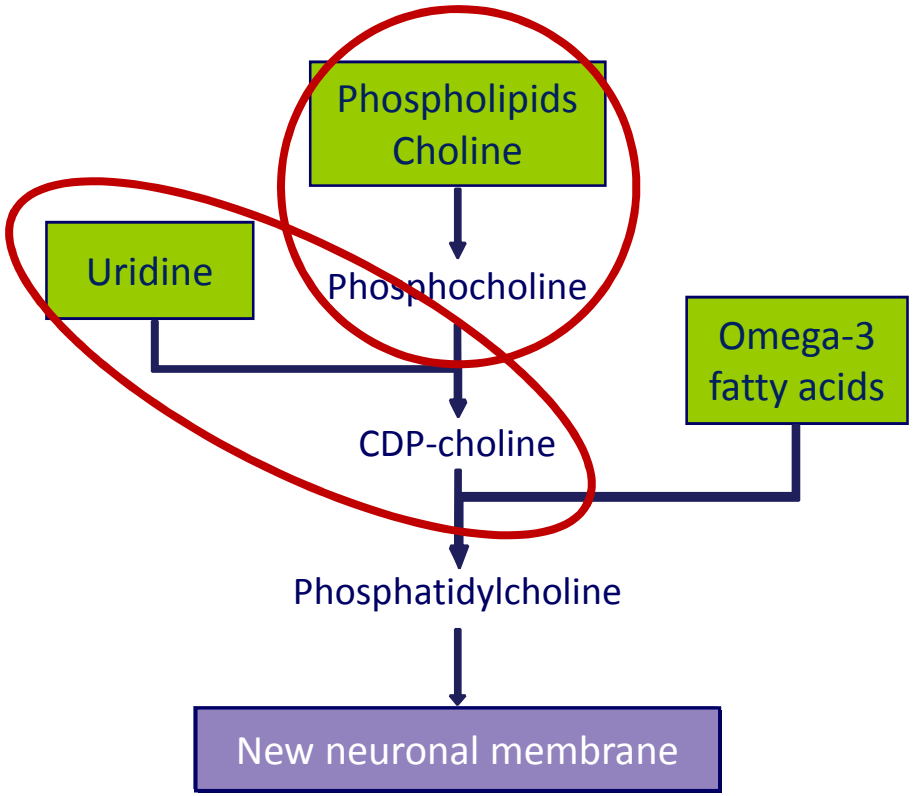


Membranes are main constituents of synapses

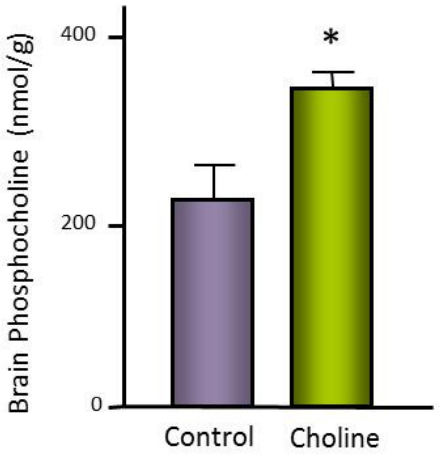


Dietary precursor control of neural membrane synthesis

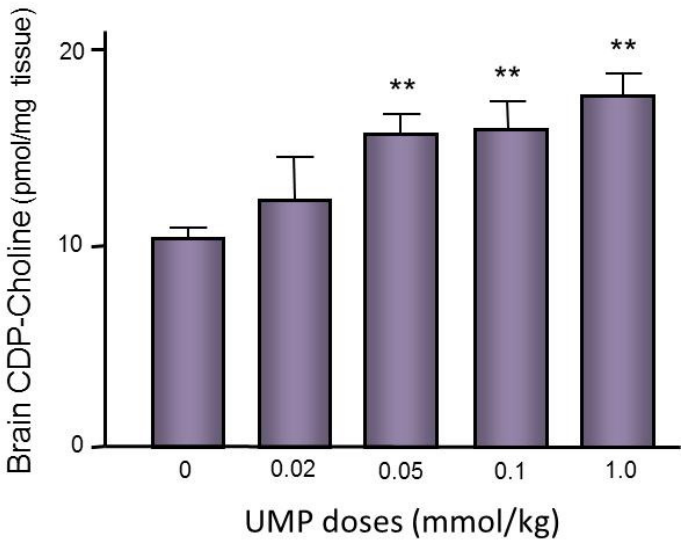
The Kennedy pathway for biosynthesis neuronal membrane



Kennedy & Weiss (1956) J Biol Chem

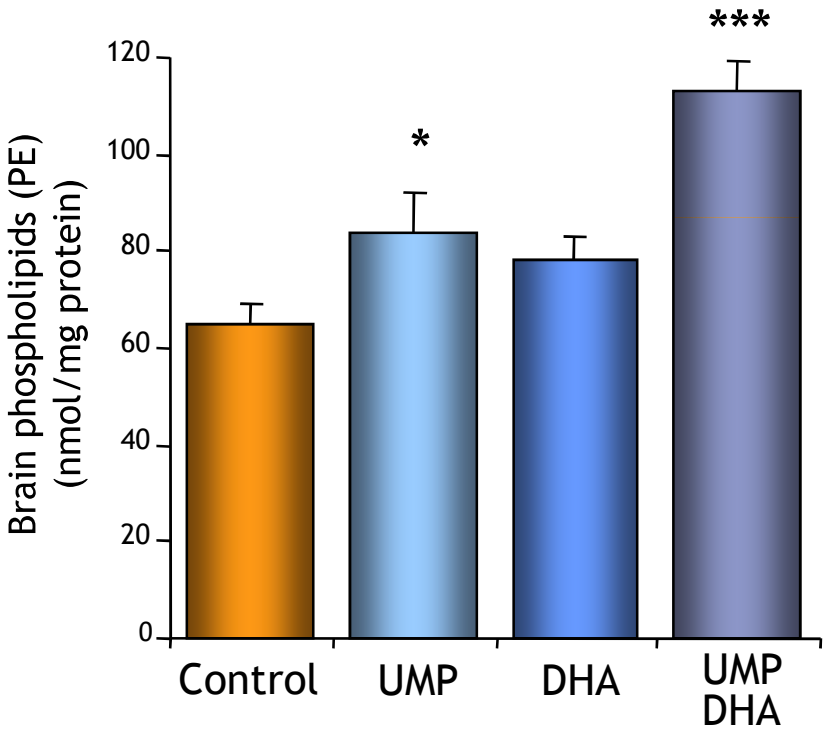


Millington & Wurtman (1982) J Neurochem



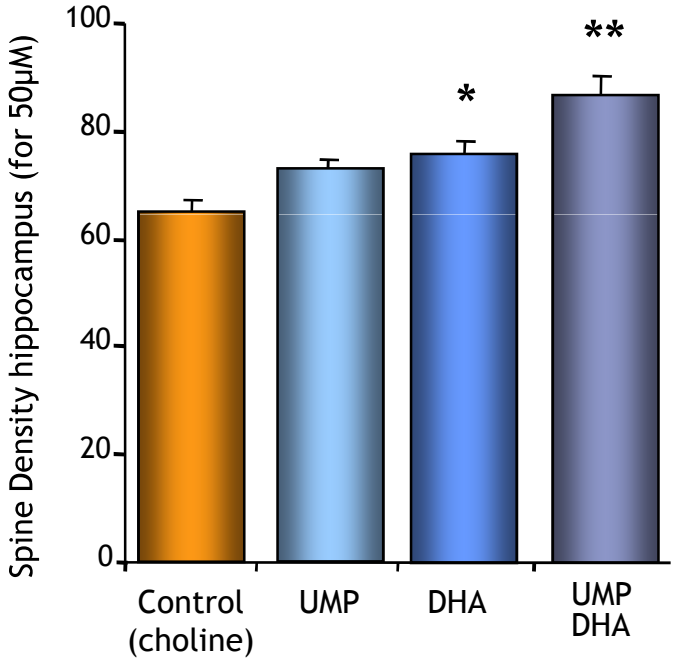
Cansev et al (2005) Brain Res

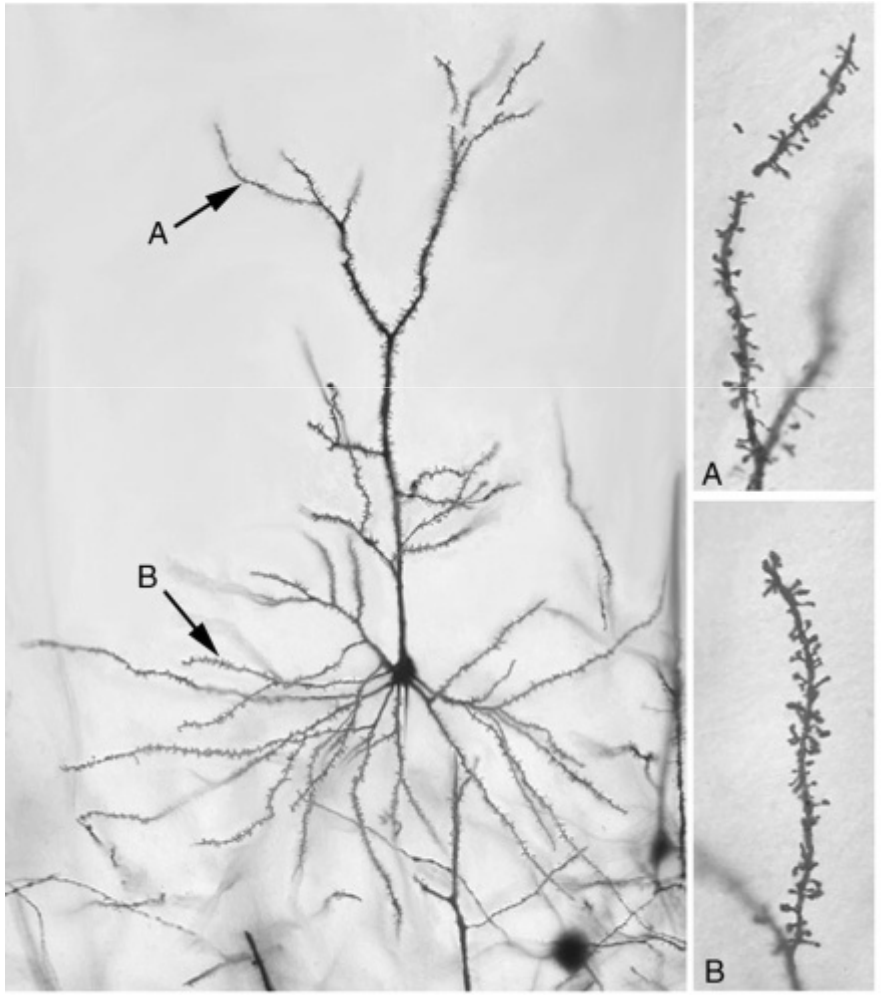
Dietary precursors can be rate-limiting: Synergy between dietary precursors



Wurtman et al (2005, 2006) Brain Res

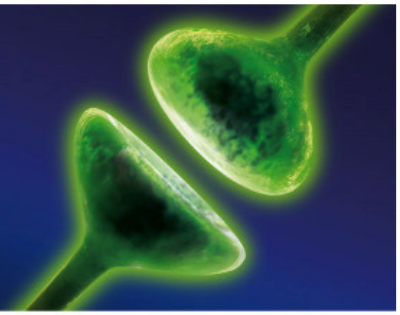
Dietary precursors increase membrane dominant structures: Dendritic spines

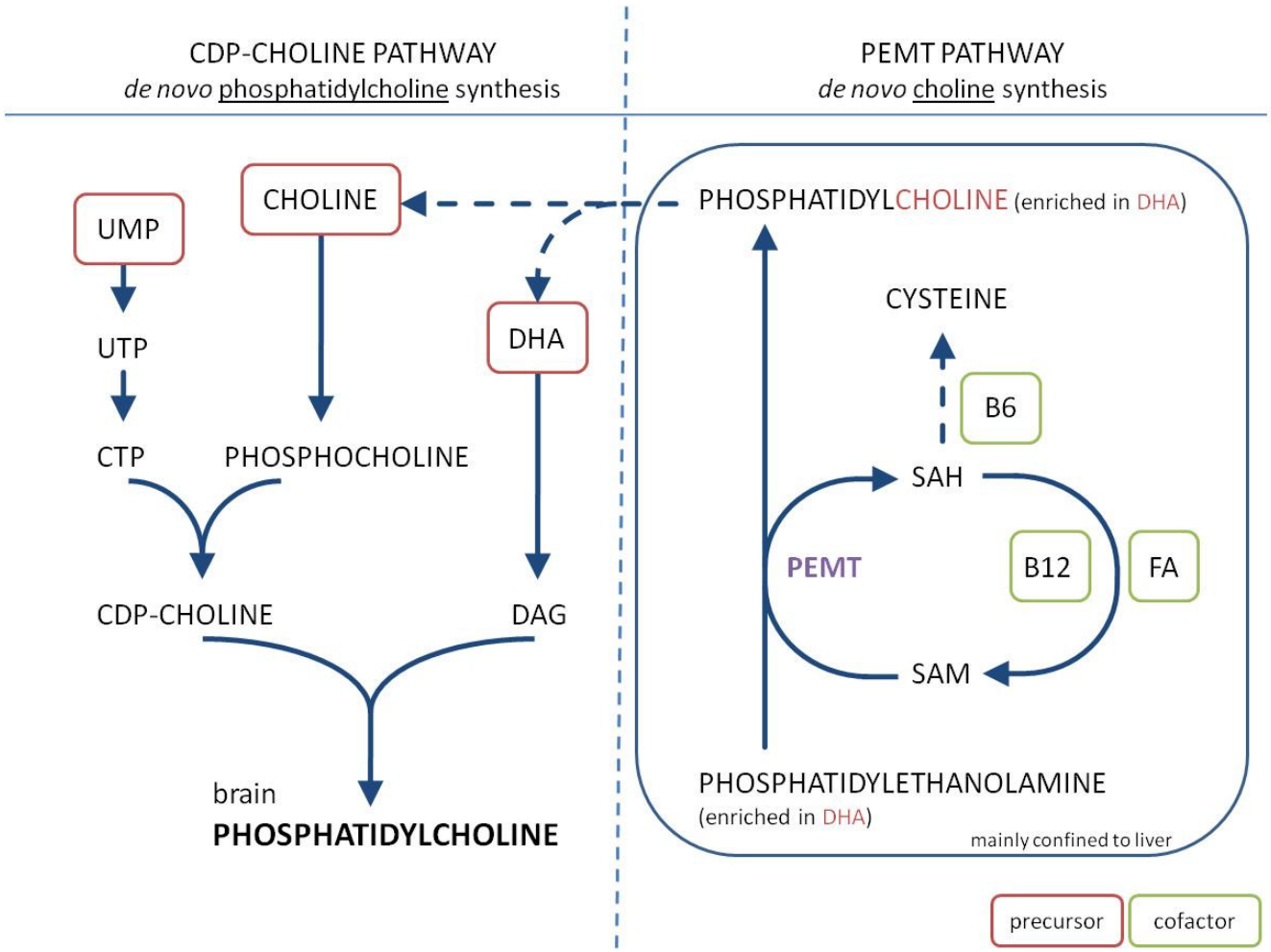




Sakamoto et al (2007) Brain Res

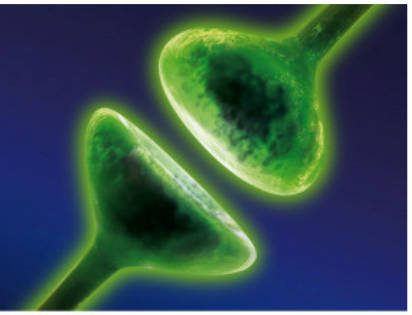
B-vitamins: cofactors for endogenous production of membrane precursors



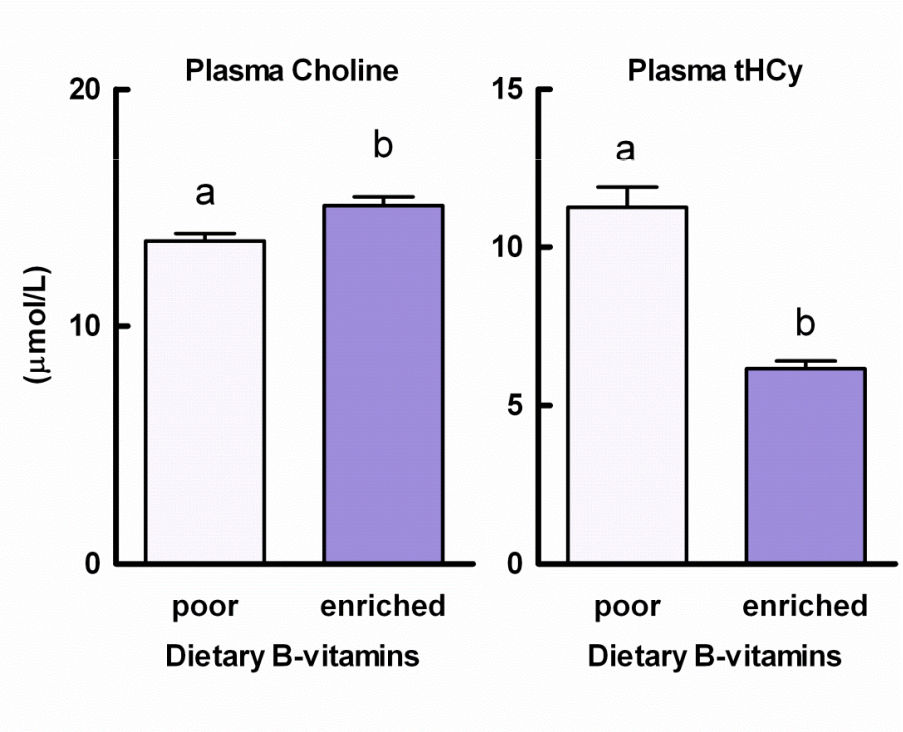


PEMT = phosphatidylethanolamine-N-methyltransferase

Precursor availability: B-vitamins increase plasma choline and DHA

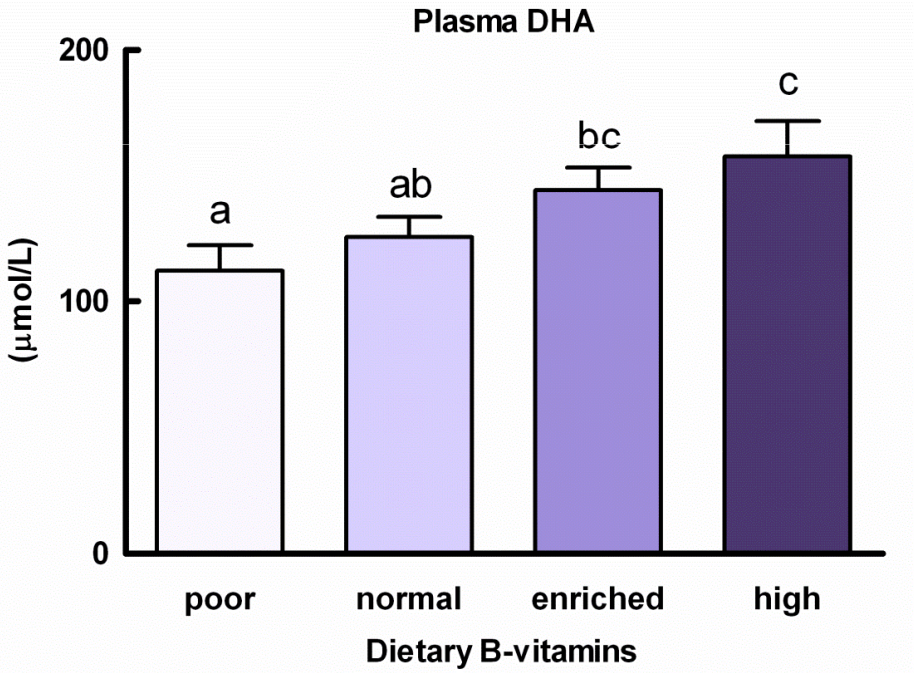


B vitamins increase choline



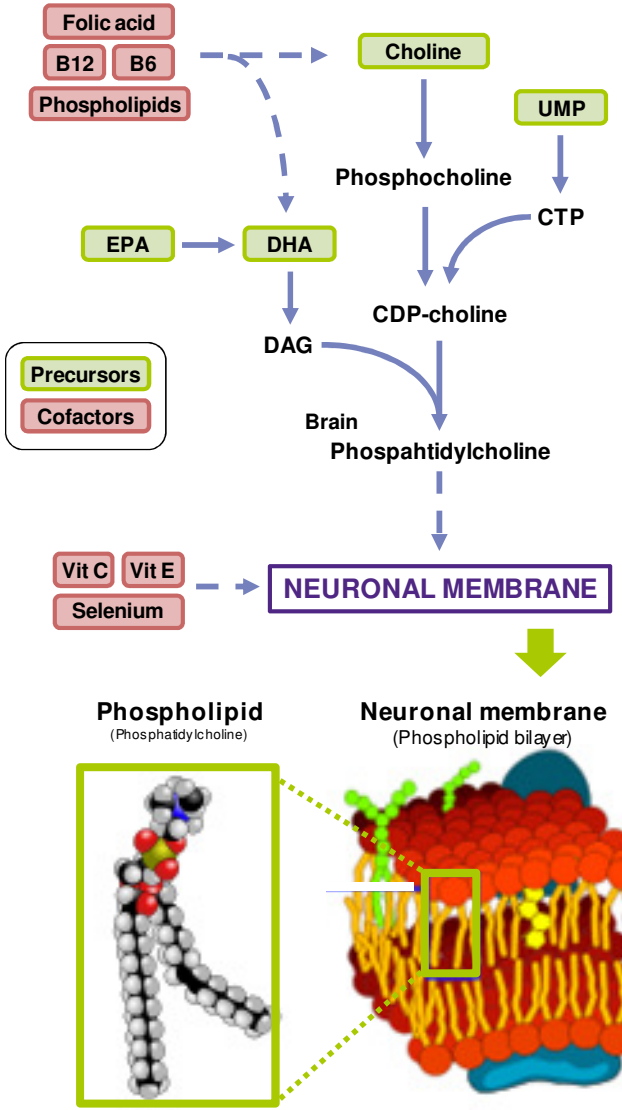
van Wijk et al (2011) Br J Nutr

B vitamins dose-dependently increase DHA

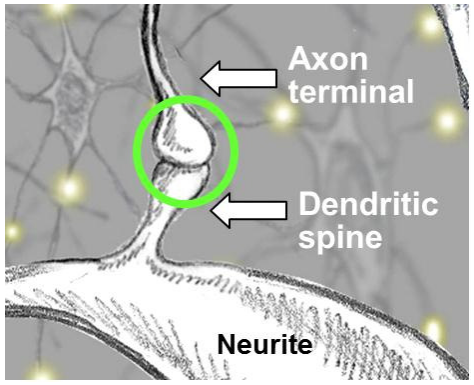


van Wijk et al (2012) Nutr Metabol

Nutritional precursors and cofactors: enhanced availability by Fortasyn Connect



- Synapses are continuously being remodeled
- Synapses are part of the neuronal membrane
- Membranes consist of phospholipids
- Phospholipid synthesis depends on the presence of uridine, choline and DHA
- B-vitamins enhance precursor bioavailability
- Antioxidants protect the neuronal membrane and maintain its integrity, stability and function



Precursors and cofactors enhance synapse formation and function – basic science data

Journal of Alzheimer's Disease 38 (2014) 459–479
DOI 10.3233/JAD-130998
IOS Press

nnect

Review

Targeting Synaptic Dysfunction in Alzheimer's Disease by Administering a Specific Nutrient Combination

Nick van Wijk[a,*], Laus M. Broersen[a], Martijn C. de Wilde[a], Robert J.J. Hageman[a], Martine Groenendijk[a], John W.C. Sijben[a] and Patrick J.G.H. Kamphuis[a,b]
[a]*Nutricia Advanced Medical Nutrition, Nutricia Research, Utrecht, The Netherlands*
[b]*Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands*

3

8

8

3,29

9-31

- Improve learning & memory / behavior ✓ 11,13-17 ✓ 19,22,29-31

1.Cansev (2005) Brain Res
2.Ulus (2006) Cell Mol Neurobiol
3.Van Wijk (2011) Br J Nutr
4.Van Wijk (2012) Nutr Metab
5.Wurtman (2006) Brain Res
6.Wang (2005) J Mol Neurosci
7.Pooler (2005) Neuroscience
8.Sakamoto (2007) Brain Res
9.Farkas (2002) Brain Res
10.Wang (2007) Brain Res
11.Kariv-Inbal (2012) JAD
12.Grimm (2011) JBC
13.Teather (2003) PNBP
14.de Wilde (2003) Brain Res
15.de Wilde (2002) Brain Res
16.de Bruin (2003) J Learn Mem
17.Holguin (2008) BehavBrainRes
18.van Wijk (2014) JAD
19.de Wilde (2011) J Alz Dis
20.Cansev (2012) data on file
21.Cansev (2013) data on file
22.Jansen (2013) PLOS ONE
23.Broersen (2013) J Alz Dis
24.Savelkoul (2012) AAIC
25.Zerbi (2013) Neurobiol Aging
26.Savelkoul (2011) ADPD
27.Verheijen (2012) data on file
28.Savelkoul (2012) J Neurochem
29.Jansen (2013) Brain Struc Fun
30.Koivisto (2013) in press
31.Wiesmann (2013) JAD

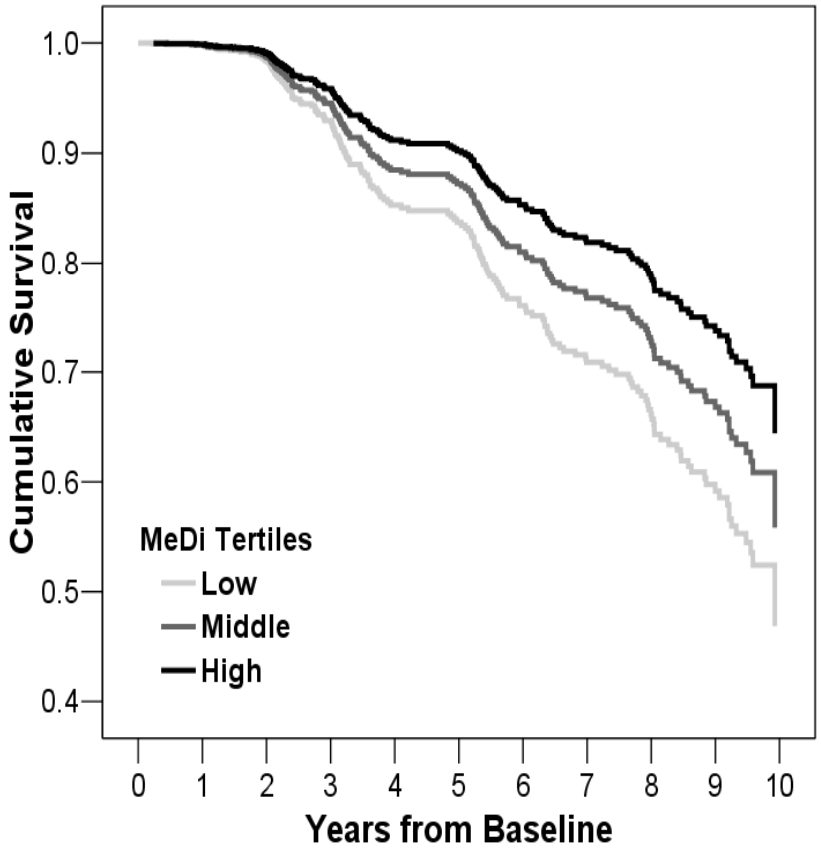
AD risk and nutrient intake

Observational studies suggest a link between Mediterranean diet & AD risk, but data not fully consistent

Mediterranean diet:

- High vegetables, legumes, fruits, and cereals
- High unsaturated fatty acids
- Low saturated fatty acids
- Moderately high fish
- Low-to-moderate dairy
- Low meat and poultry
- Regular but moderate amount of ethanol, primarily in the form of wine and generally, during meals

AD incidence by diet tertile

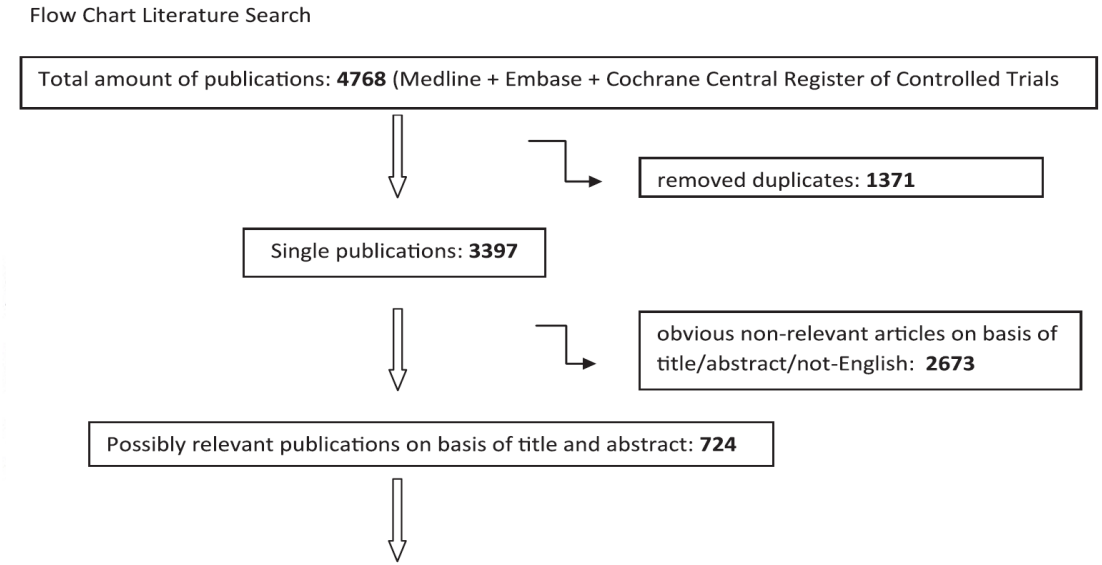


Scarmeas et al (2006) Ann Neurol

Scarmeas et al, *Ann Neurol,* 2006; Psaltopoulou et al, *Public Health Nutr,* 2008;
Feart et al, *JAMA*, 2009; Cherbuin et al, *Am J Geriatr* Psychiatry, 2011; Tangney et al, *Am J Clin Nutr*, 2011

Systematic review and meta-analysis on nutrient availability in AD

- According to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines
- Analyses by independent statisticians



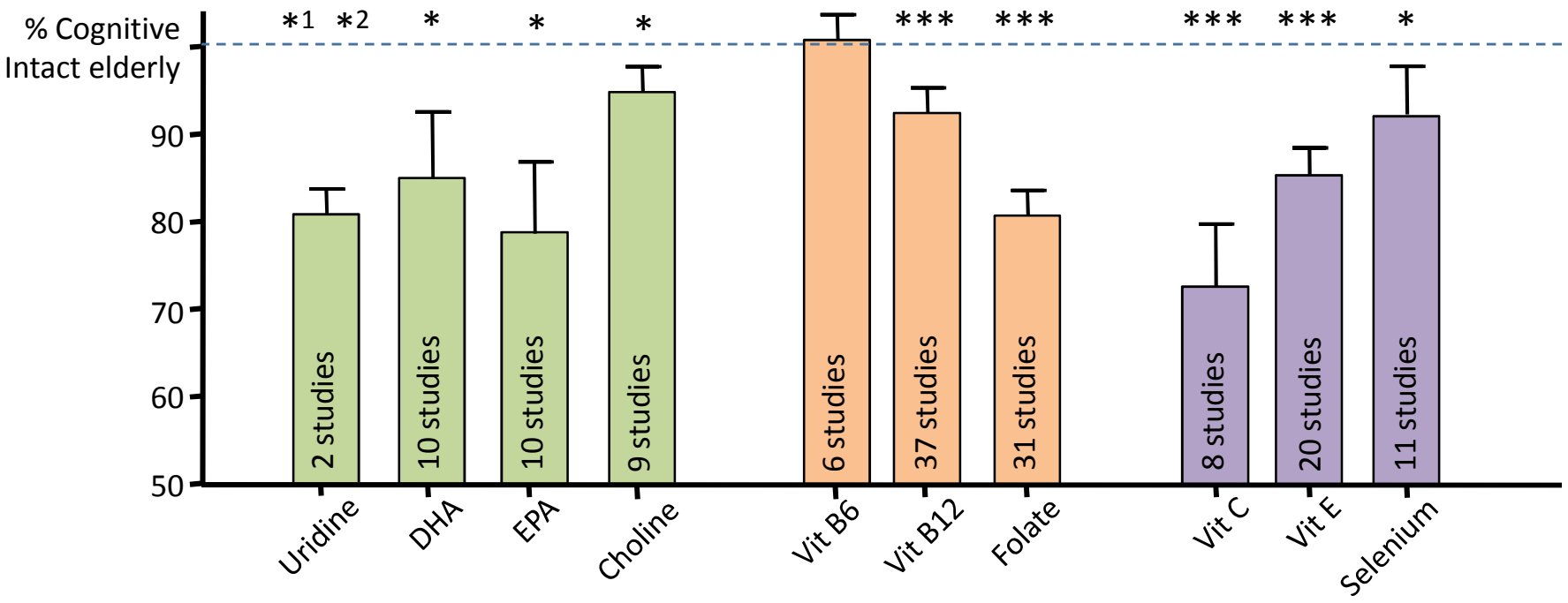
Alzheimer's & Dementia

Plasma nutrient status of patients with Alzheimer's disease: Systematic review and meta-analysis

Sofia Lopes da Silva[a,b], Bruno Vellas[c], Saskia Elemans[a], José Luchsinger[d], Patrick Kamphuis[a,b], Kristine Yaffe[e], John Sijben[a,*], Martine Groenendijk[a], Theo Stijnen[f]

Systematic review and meta-analysis of literature: Lower plasma levels of precursors & cofactors in AD

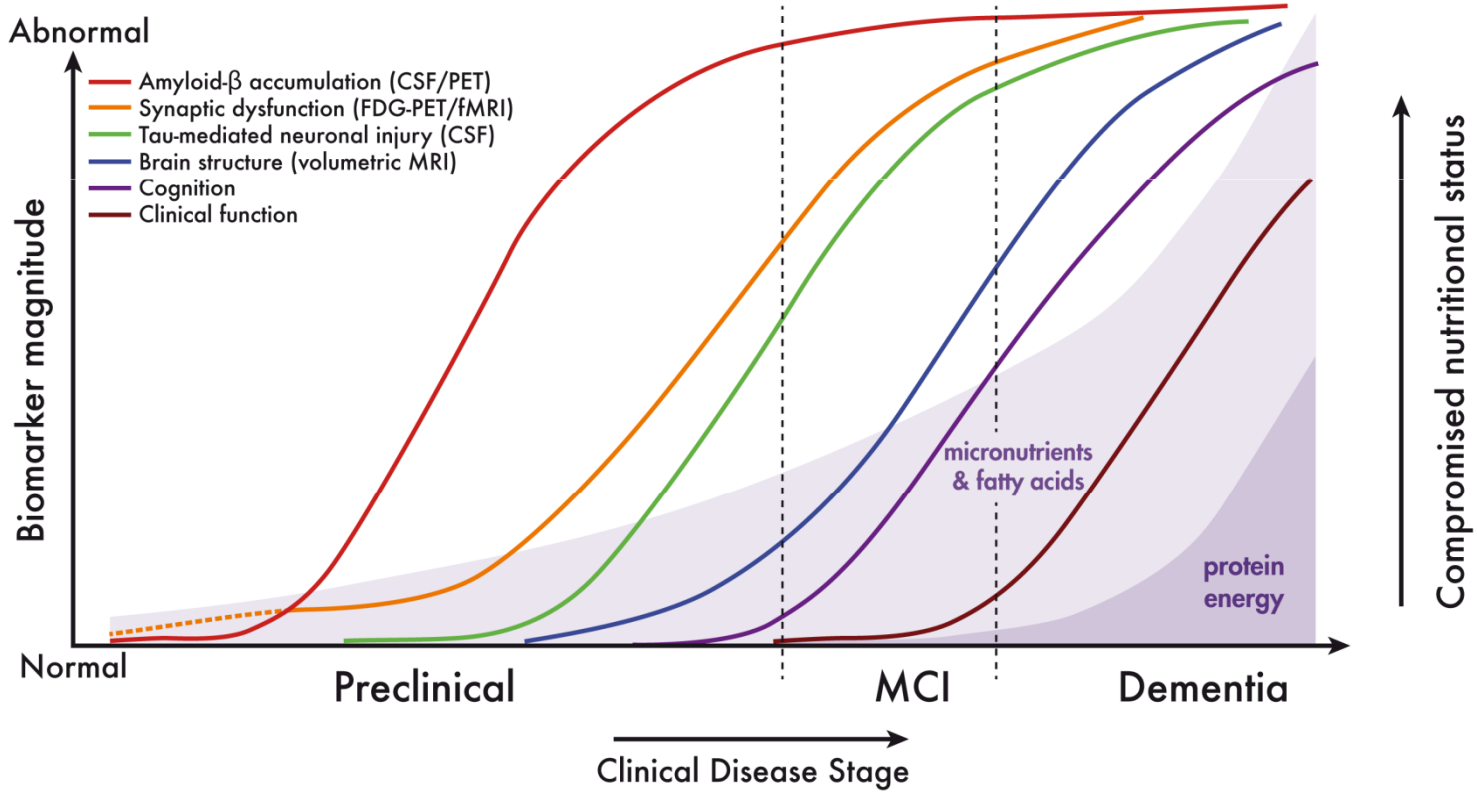
Plasma nutrient status in AD
Meta-analyses, systematic review and observations



1:Trushina (2013) PLOS 2:Olde Rikkert (2013)ADPD	Meta-analyses Lin (2012) JCP	Meta-analyses data on file	Meta-analyses Lopes da Silva (2013) Alz Dement	Systematic review Loef (2011) JAD

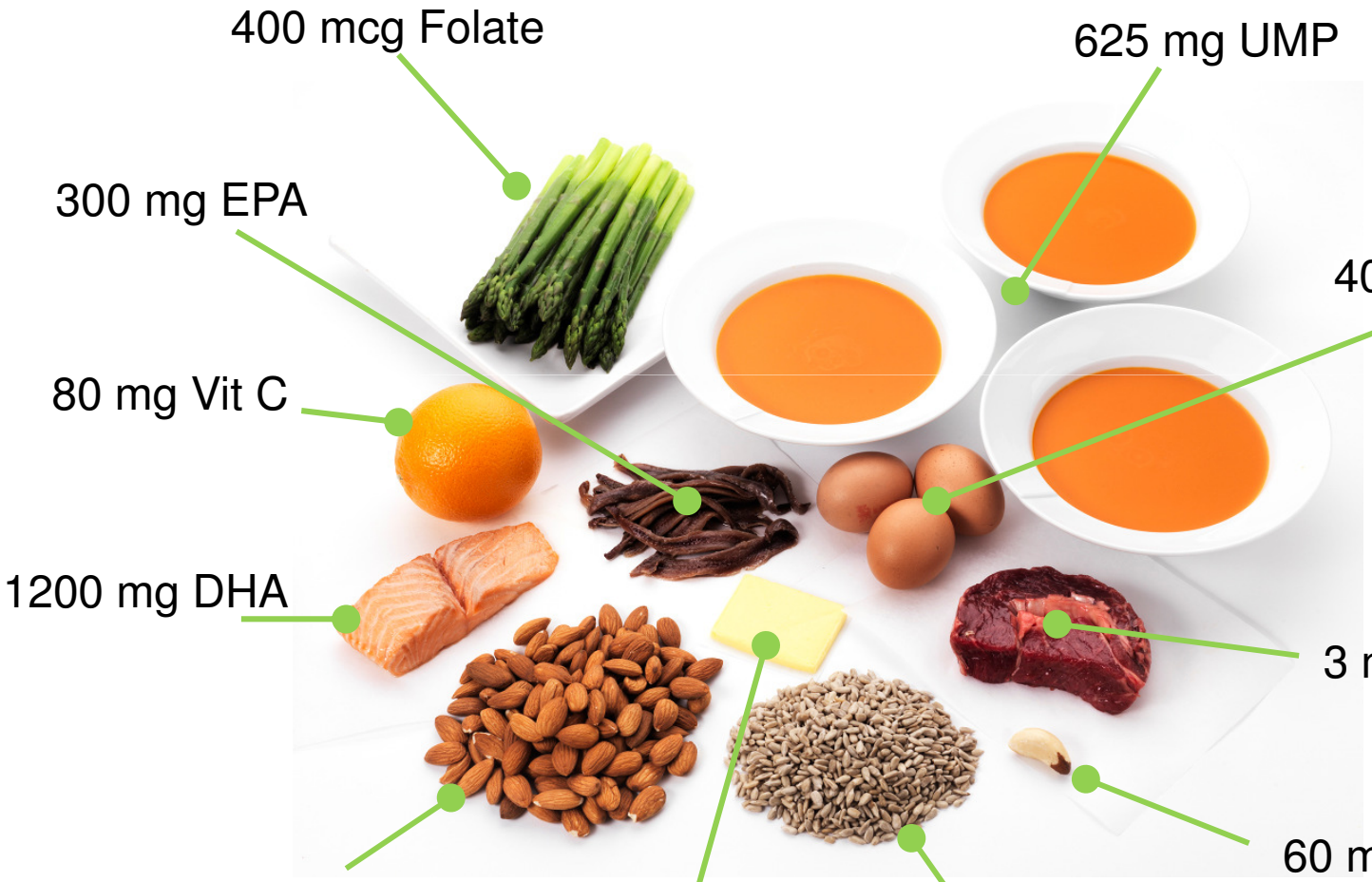
Lower nutrient status preceding classic protein energy malnutrition

Epidemiological relate dietary patterns with AD risk

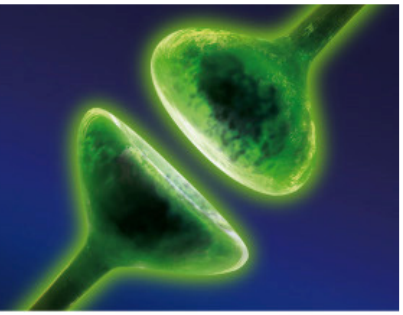


Mi et al (2013) Nutrition

Development of Souvenaid: addressing AD specific requirements



Souvenaid Clinical Development

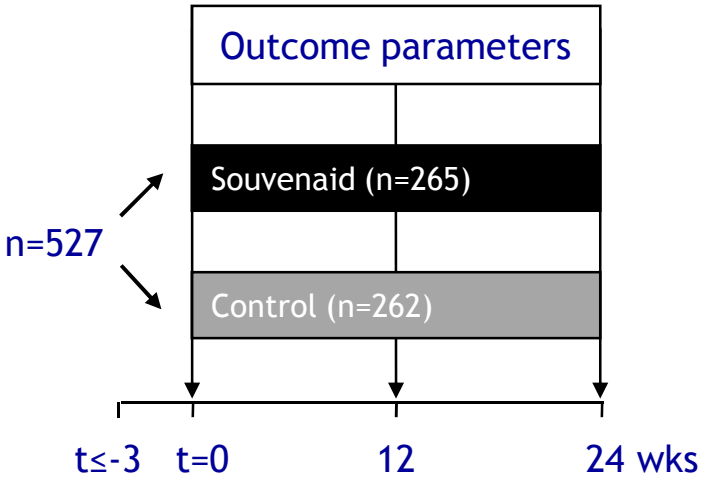


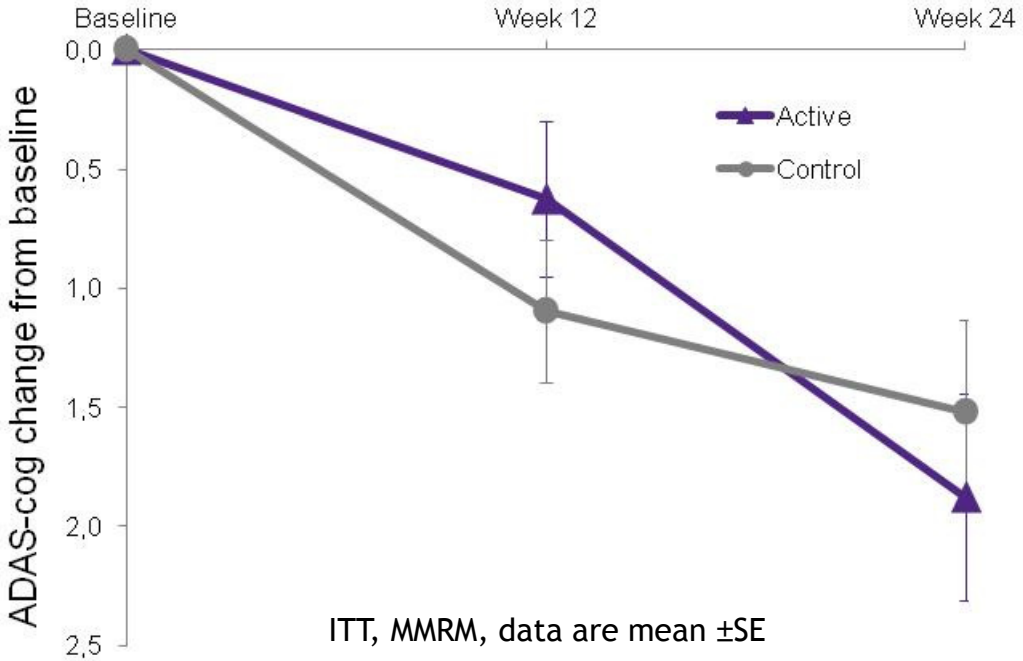
	Prodromal AD	Mild AD	Moderate AD
S-Connect			ADAS-cog MMSE 14-24, stable on AD drugs
Souvenir I		WMS-r & ADAS-cog MMSE 20-26, drug-naïve	
Souvenir II		NTB + EEG MMSE ≥ 20, drug-naïve	
Open Label		Safety + Compliance + NTB	
MEG study		MEG + EEG +NTB MMSE ≥ 20, drug-naïve	
MRS study		^{31}P and ^{1}H-MRS MMSE ≥ 20, drug-naïve	
NL-Enigma	^{18}FDG-PET MMSE ≥ 20, drug-naïve		
LipiDiDiet	NTB + MRI / CSF MMSE ≥ 24, drug-naïve		

Souvenir I received funding from NL STW
Souvenir II receives funding from the NL Food & Nutrition Delta project, FND N°10003
LipiDiDiet is funded by the EU FP7 project LipiDiDiet, Grant Agreement N° 211696
NL-Enigma funded by NWO NIHC project, N°057-13-003.

S-Connect study: mild to moderate AD on AD medication

- Principle investigators: David Bennett and Raj Shah, Rush, Chicago
- Multi-centre (48 sites in the US), randomized, controlled trial
- Intervention 24 weeks
- Primary outcome:
  - ADAS-cog-11





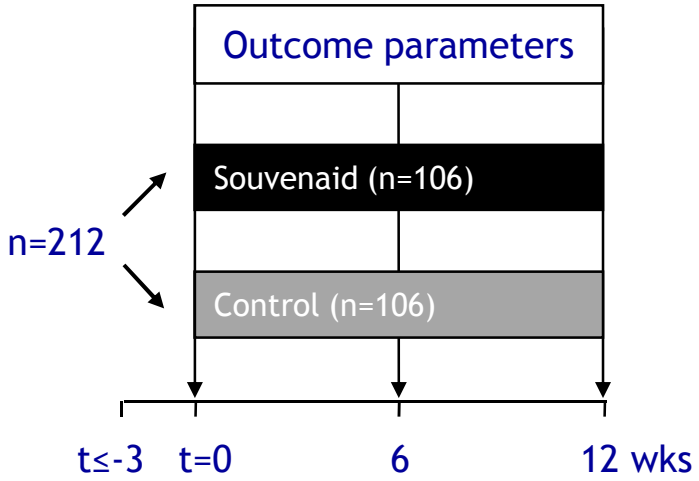
ITT, MMRM, data are mean ±SE

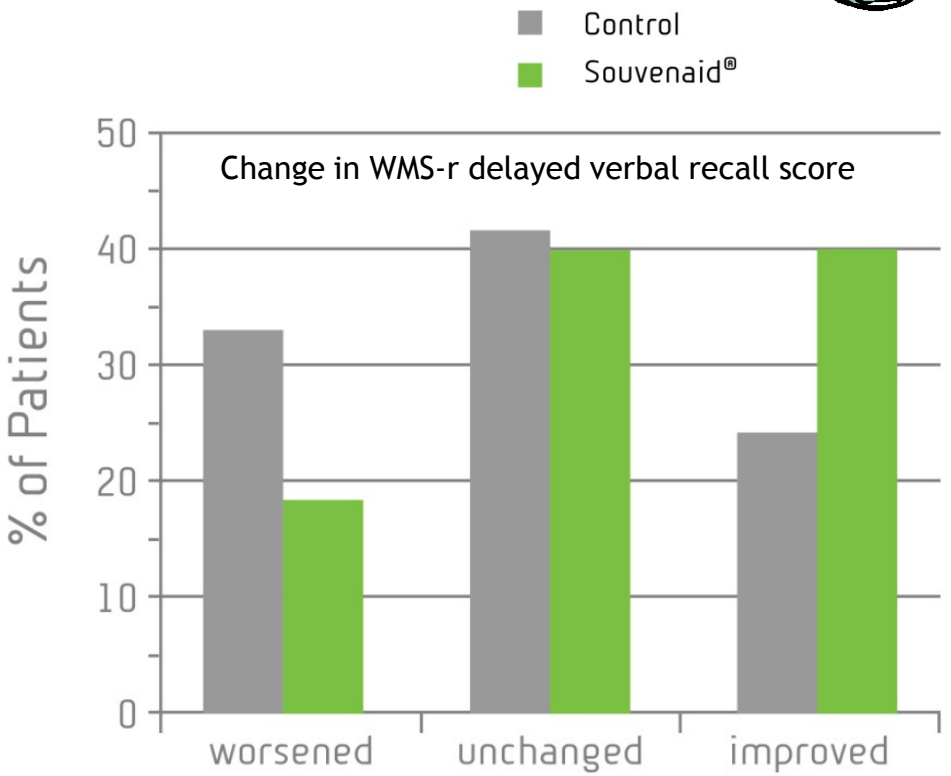
No significant effect (p=0.513) during 24 weeks

Shah et al (2013) Alz Res Ther

Souvenir I: Proof of concept study in drug-naive mild AD

- Multi-country (NL, Bel, Ger, UK, US), randomized, controlled trial
- Intervention 12 weeks *(+ optional 12 wk extension)*
- Co-primary outcomes:
  - WMS-r delayed verbal recall
  - ADAS-cog-13



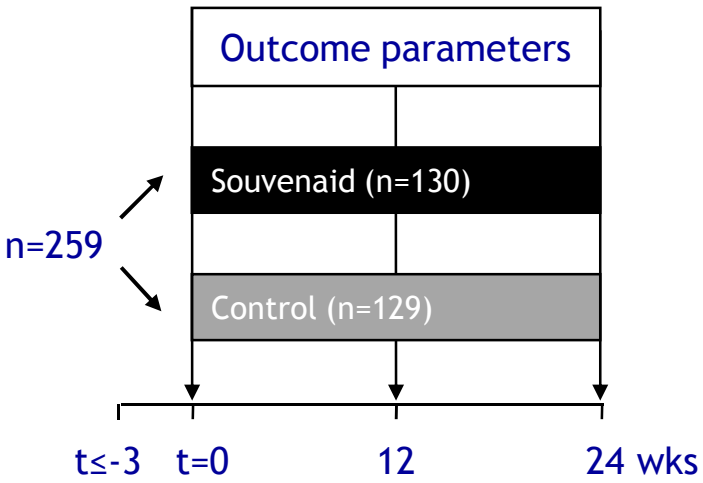


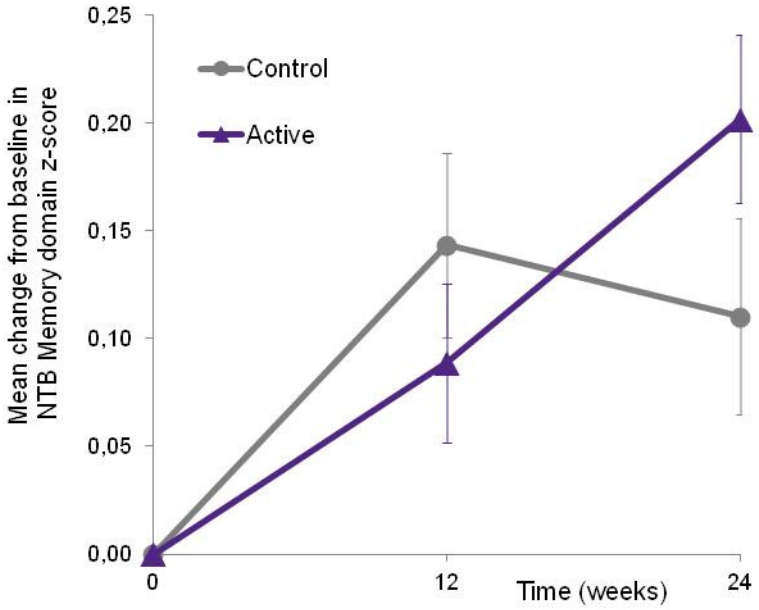
Significantly more responders after 12 weeks (p=0.021)

Scheltens et al (2010) Alzh Dement

Souvenir II study: drug-naive mild AD

- Multi-country (NL, Ger, Bel, Fr, It, Sp), randomized, controlled trial
- Intervention 24 weeks
- Primary outcome: Memory Domain NTB (z-score):
  - RAVLT immediate, delayed, recognition and VPA immediate and delayed

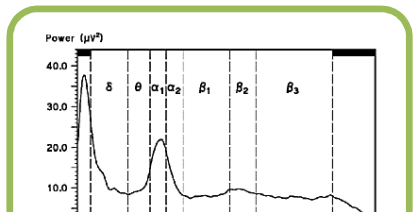


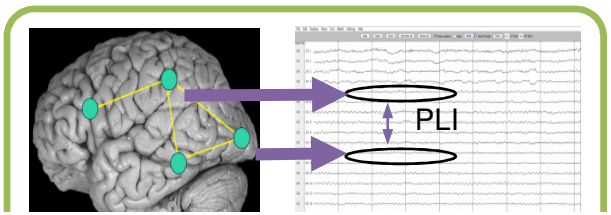


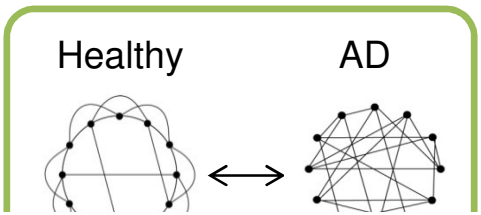
Significantly improved memory (p=0.023)
Memory domain score (z-score) of NTB

Scheltens et al (2012) J Alzheimers Dis

Electrical activity at the synapse – EEG biomarker for functional connectivity







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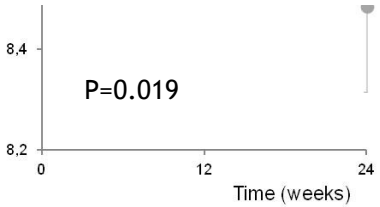
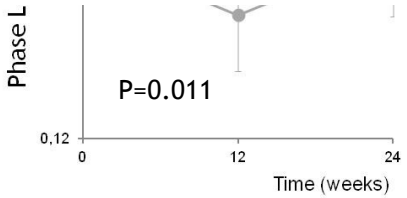
PLOS ONE

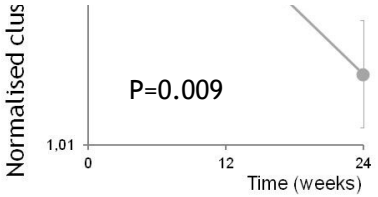
The Effect of Souvenaid on Functional Brain Network Organisation in Patients with Mild Alzheimer's Disease: A Randomised Controlled Study

Hanneke de Waal[1]*, Cornelis J. Stam[2], Marieke M. Lansbergen[3], Rico L. Wieggers[3], Patrick J. G. H. Kamphuis[3], Philip Scheltens[1], Fernando Maestú[4], Elisabeth C. W. van Straaten[2,3]

1 Alzheimer Center & Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands, **2** Department of Clinical Neurophysiology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands, **3** Nutricia Research, Utrecht, The Netherlands, **4** Laboratory of Cognitive and Computational Neuroscience, UCM-UPM Center for Biomedical Technology, Madrid, Spain





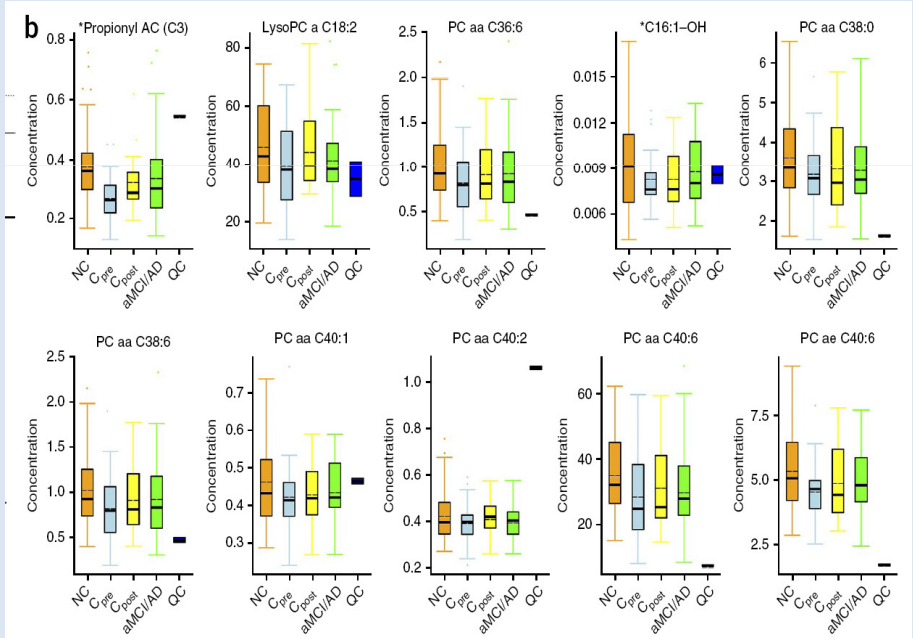


Scheltens et al (2012) J Alzheimers Dis; de Waal et al (2014) PlosOne

Plasma phospholipids identify antecedent memory impairment in older adults

Mark Mapstone[1], Amrita K Cheema[2,3], Massimo S Fiandaca[4,5], Xiaogang Zhong[6], Timothy R Mhyre[5], Linda H MacArthur[5], William J Hall[7], Susan G Fisher[8,14], Derick R Peterson[9], James M Haley[10], Michael D Nazar[11], Steven A Rich[12], Dan J Berlau[13,14], Carrie B Peltz[13], Ming T Tan[6], Claudia H Kawas[13] & Howard J Federoff[4,5]

NATURE MEDICINE



- set of 10 plasma lipids, including 8 phospholipids
- levels are lower in converters and MCI/AD subjects

- Mapstone et al. identified a biomarker panel of 10 plasma lipids that can predict conversion from cognitive healthy to MCI/AD within 2-3 years with >90% accuracy
- Changes may reflect the breakdown of neuronal membranes
- Highly publicitized findings

The Washington Post

Blood test may predict onset of Alzheimer's and related disease, new study finds

By Tara Bahrampour, E-mail the writer

Researchers at Georgetown University announced the discovery of a blood test that can predict whether a person will develop Alzheimer's disease or a related condition within three years.

BMJ

Blood test can predict Alzheimer's disease, say US scientists

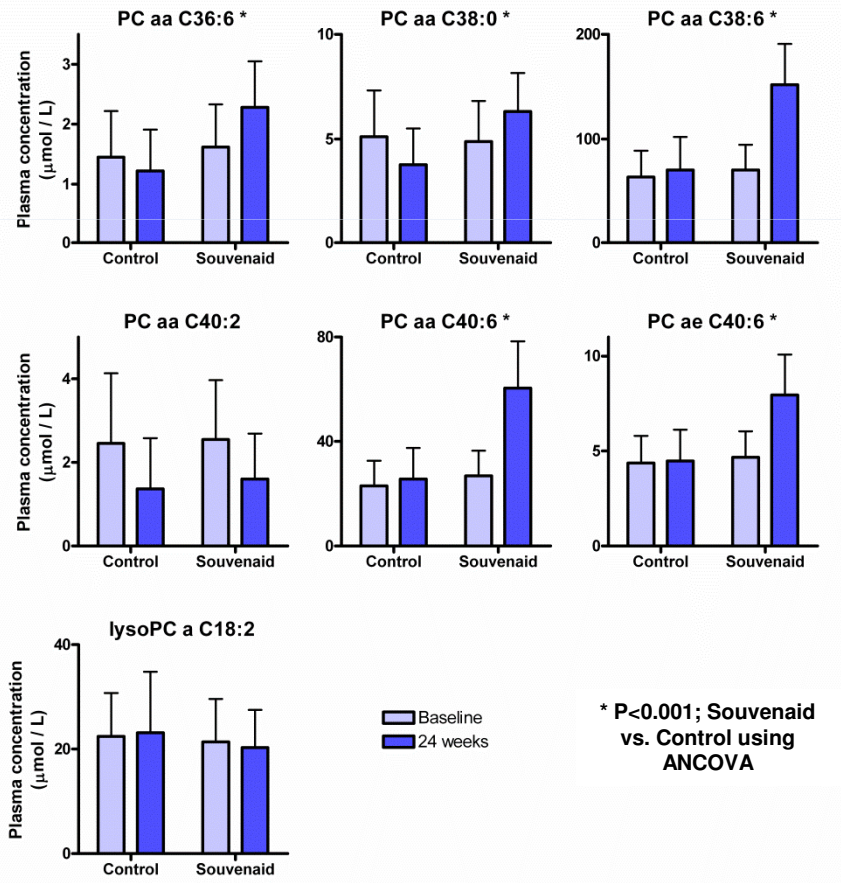
Jacqui Wise

Souvenaid increases levels of the biomarker phospholipids

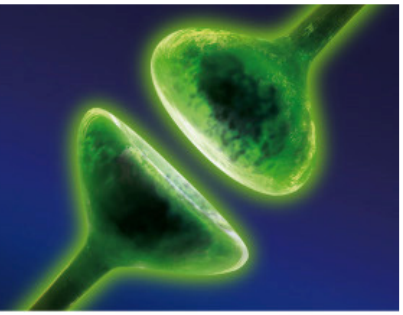
- Baseline and 24-week plasma samples from the Souvenir II study
- Drug-naïve patients with very mild AD
- Polar lipid profile

- By providing nutrients which normally rate-limit phospholipid synthesis Souvenaid can:
  - modify a biomarker profile reflecting disturbed phospholipid metabolism
  - be useful in asymptomatic subjects with plasma lipid biomarker profiles predictive for conversion to AD

5 / 7 measured phospholipids reported by Mapstone significantly increased by Souvenaid



Souvenaid Clinical Development



	Prodromal AD	Mild AD	Moderate AD
S-Connect			ADAS-cog MMSE 14-24, stable on AD drugs
Souvenir I		WMS-r & ADAS-cog MMSE 20-26, drug-naïve	
Souvenir II		NTB + EEG MMSE ≥ 20, drug-naïve	
Open Label		Safety + Compliance + NTB	
MEG study		MEG + EEG +NTB MMSE ≥ 20, drug-naïve	
MRS study		^{31}P and ^{1}H-MRS MMSE ≥ 20, drug-naïve	
NL-Enigma	^{18}FDG-PET MMSE ≥ 20, drug-naïve		
LipiDiDiet	NTB + MRI / CSF MMSE ≥ 24, drug-naïve		

Souvenir I received funding from NL STW
Souvenir II receives funding from the NL Food & Nutrition Delta project, FND N°10003
LipiDiDiet is funded by the EU FP7 project LipiDiDiet, Grant Agreement N° 211696
NL-Enigma funded by NWO NIHC project, N°057-13-003.


Thank you!
NUTRICIA
Souvenaid®